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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/581,602	01/09/2007	Ji Sook Park	1751-409	3620

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ART UNIT	PAPER NUMBER
1646	

NOTIFICATION DATE	DELIVERY MODE
08/24/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PTO-PAT-Email@rfem.com

Office Action Summary	Application No.	Applicant(s)	
	10/581,602	PARK ET AL.	
	Examiner	Art Unit	
	Bruce D. Hissong, Ph.D.	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 May 2009 and 07 August 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/28/09 and 8/7/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Formal Matters

1. Applicants' response to the office action mailed on 2/24/2009, including arguments/remarks and amended claims, was received on 5/26/2009 and has been entered into the record.

2. Claims 1-5 are pending and are the subject of this office action.

Information Disclosure Statement

1. The information disclosure statement received on 4/28/2009 has been fully considered.

2. The information disclosure statement received on 8/7/2009 has been fully considered. Citations 1-3 have been lined-through because these citations were previously cited in the information disclosure statement received on 1/9/2007.

Claim Objections

Objection to claim 4, as set forth on page 2 of the office action mailed on 2/24/2009, is *withdrawn* in view of Applicants' amendments to the claim to an "ultrafiltration membrane with a molecular weight cut-off of 10,000 daltons".

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Rejection of claim 4 under 35 USC § 112, second paragraph, as being indefinite regarding the molecular weight units for the cut-off of the cited ultrafiltration membrane, as set forth on page 2 of the office action mailed on 2/24/2009, is *withdrawn* in response to Applicants' amendments to the claim to recite "an ultrafiltration membrane with a molecular weight cut-off of 10,000 daltons".

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-5 *remain rejected* under 35 USC § 103(a) as being obvious in view of the combination of Utsumi *et al* ("Utsumi" – *Eur. J. Biochem.*, 1989, Vol. 181, p. 545-553), Carter *et al* ("Carter" – US 4,483,849), and Revel *et al* ("Revel" - US 4,808,523), as set forth on pages 3-5 of the office action mailed on 2/24/2009.

The claims of the instant invention are drawn to a process for purifying human interferon beta (IFN-β) from a recombinant IFN-β-containing culture, wherein said method comprises performing affinity chromatography and reverse-phased high-performance liquid chromatography (RP-HPLC). The claims are further drawn to methods of affinity chromatography comprising washing with various buffer solutions comprising a range of propylene glycol concentrations and at cited ranges of pH, wherein said buffers further comprise sodium chloride, and wherein said buffers comprise sodium or potassium phosphate. Also claimed is said process for purifying IFN-β, wherein said process further comprises ultrafiltration of the solution obtained by affinity chromatography with an ultrafiltration membrane of molecular weight cut-off of 10,000 daltons, and subsequently loading an IFN-β-containing fraction on an RP-HPLC column.

Utsumi teaches a method of purifying human recombinant IFN-β from culture fluid, wherein said method comprises loading said IFN-β-containing cell culture fluid onto an affinity column (blue Sepharose CL-6B), followed by washing and elution with a 20 mM phosphate buffer, pH 7.4, and further affinity purification using a column of anti-IFN-β-specific antibody. The resulting solution was then further purified by RP-HPLC (see p. 546, 1st column – "Purification of HuIFN-β1s"). Utsumi is silent regarding the use of propylene glycol-containing buffers.

However, Carter discloses a method of purifying IFN-β comprising affinity chomatography using propylene glycol-containing buffers (see Example 1; see also claims 1-5). Specifically, Carter teaches purification of IFN-β-containing fluid using an equilibrated Affi-Gel Blue column, which is taught by the present specification to be an affinity purification column (see paragraphs 0090-0011). Carter also discloses washing and elution with sodium phosphate buffers containing 40-50% propylene glycol (see

Example 1, 2nd paragraph). Carter specifically teaches that solutions containing ethylene glycol are toxic, and therefore the use of ethylene glycol is not desirable in the purification of therapeutic agents. In contrast, propylene glycol is not toxic and also yields higher concentrations of IFN-β when used in methods of purification (column 1, line 25 - column 2, line 52).

Similarly, Revel also teaches purification of recombinant human IFN-β by affinity chromatography using a Blue-Sepharose column, followed by elution with 20 mM phosphate buffer, pH 7, containing 40% propylene glycol (see column 13, line 60 - column 14, line 17; see also claims 2, 7, and 8). Revel also teaches concentration of affinity-purified IFN-β by ultrafiltration with a YM10 membrane, which is known in the art to have a molecular weight cut-off of 10,000 daltons (see Millipore catalog - http://www.millipore.com/catalogue/itemdetail.do?id=13622 – this citation is not being used in a grounds of rejection, but to point out a physical property of YM10 ultrafiltration membranes).

In the response received on 5/26/2009, the Applicants argue that the presently claimed invention is not obvious in view of the combination of Utsumi, Carter, and Revel because none of the cited references teaches or suggests a method utilizing two different wash solutions, with one wash solution (A) having pH of 6.5-7.5 and containing 30-60 wt% propylene glycol, and another wash solution (B) having a pH of 6.5-7.5 and containing 10-30 wt% propylene glycol and 1-2 M NaCl, as is required by the instant claims. Specifically, the Applicants note that while Utsumi discloses a wash solution comprising 2 M NaCl and 30% propylene glycol, it does not teach or suggest a wash solution comprising only propylene glycol. Similary, both Carter and Revel teach methods using single wash buffers, with Carter's wash buffer comprising 40% propylene glycol and Revel's buffer comprising 40% propylene glycol and 1 M NaCl, the latter of which was used to elute, rather than wash the affinity columns. Therefore, because none of the cited references teach or suggest methods of IFN-β isolation comprising affinity chromatography followed by two separate washes, the present claims are not obvious in view of the combination of Utsumi, Carter, and Revel.

These arguments have been fully considered and are not persuasive. As set forth in the previous office action, Utsumi, Carter, and Revel teach methods of IFN-β purification utilizing affinity chromatography, with Carter and Revel using wash and elution buffers comprising propylene glycol, and Utsumi also disclosing further purification using RP-HPLC. Regarding the use of propylene glycol, Carter specifically discloses that propylene glycol is useful in methods of IFN-β purification because it is non-toxic and elution with propylene glycol results in increased IFN-β yield (column 2, lines 21-40). Additionally, Carter also teaches that propylene glycol is useful because it stabilizes IFN-β (column 2, lines 41-45). Therefore, a person of ordinary skill in the art would have ample motivation to practice a

method of IFN-β purification which comprises affinity chromatography followed by RP-HPLC, wherein the affinity column is washed with buffers comprising propylene glycol. Indeed, Revel teaches that IFN-β purified by affinity chromatography should be washed with "a suitable solution to remove the proteins other than the IFN-β which have not been absorbed" (column 2, lines 30-33; see also column 4, lines 32-35). Thus, a person of ordinary skill in the art would know that IFN-β purified by affinity chromatography should be washed using a suitable solution, and would know that solutions comprising propylene glycol are suitable for such a purpose because propylene glycol is non-toxic and stabilizes the isolated protein. Because a skilled artisan would know that a wash buffer comprising propylene glycol would stabilize the IFN-β immobilized on the affinity column, the skilled artisan would be motivated to include a first washing step with a solution comprising propylene glycol for the purpose of protein stabilization, followed by a second wash step comprising washing with the propylene glycol and 1M NaCl solutions taught by Carter and Revel as being useful for washing IFN-β bound to affinity columns.

Furthermore, as set forth previously, the general conditions of the present invention are disclosed or suggested in the combination of Utsumi, Carter, and Revel (i.e. namely that of purification of IFN-β using affinity chromatography and RP-HPLC, and the use of phosphate buffers comprising propylene glycol and NaCl, wherein said buffers are at a neutral pH). Even without the specific teachings of Carter regarding the suitability of propylene glycol from a toxicity and protein stabilization standpoint, a person of ordinary skill in the art would have the motivation to optimize the specific conditions for isolation/purification of IFN-β, including the percentage of propylene glycol, and the number of wash steps involved. MPEP 2144.05 states:

"[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 454, 105 USPQ 223, 235, (CCPA 1955).

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In*

re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-5 *remain provisionally rejected* on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-5 of co-pending Application No. 10/581,597, as set forth on pages 5-6 of the office action mailed on 2/24/2009.

In the response received on 5/26/2009, the Applicants state this rejection will be addressed once the allegedly conflicting claims have been patented. Because the claims of the '597 have not been patented, this provisional rejection is maintained for reasons of record.

Conclusion

No claim is allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bruce D. Hissong, Ph.D., whose telephone number is (571)272-3324. The examiner can normally be reached M-F from 8:30 am - 5:00 pm. If attempts to reach the examiner by telephone are

unsuccessful, the examiner's supervisor, Gary Nickol, Ph.D., can be reached at (571) 272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Bruce D. Hissong
Art Unit 1646

/Robert Landsman/
Primary Examiner, Art Unit 1647